```
     FILE 'HCAPLUS' ENTERED AT 08:52:21 ON 14 MAY 2007
L1           147 S (DOSE-DENSE)
L2        315101 S CANCER
L3        407298 S TUMOR
L4         29699 S ADENOCARCINOMA
L5        492420 S NEOPLAS?
L6           128 S L1 AND (L2 OR L3 OR L4 OR L5)
L7         16483 S DOXORUBICIN
L8         18136 S CYCLOPHOSPHAMIDE
L9         10301 S PACLITAXEL
L10         2878 S TAXANE

     FILE 'STNGUIDE' ENTERED AT 08:52:32 ON 14 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 08:53:33 ON 14 MAY 2007
L11           17 S L6 AND L7 AND L8 AND (L9 OR L10)

     FILE 'STNGUIDE' ENTERED AT 08:53:34 ON 14 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 08:53:58 ON 14 MAY 2007

     FILE 'STNGUIDE' ENTERED AT 08:53:59 ON 14 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 08:54:50 ON 14 MAY 2007

     FILE 'STNGUIDE' ENTERED AT 08:54:51 ON 14 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 09:38:21 ON 14 MAY 2007
L12         3385 S (DOSE-ESCALATION) OR (DOSE-INTENS?)
L13            0 S L12 AND (L2 AND L3 AND L4 AND L5 AND L6 AND L7 AND L8 AND (L9

     FILE 'STNGUIDE' ENTERED AT 09:38:24 ON 14 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 09:38:58 ON 14 MAY 2007
L14           27 S L12 AND (L2 AND L3 AND L4 AND L5)

     FILE 'STNGUIDE' ENTERED AT 09:38:59 ON 14 MAY 2007

     FILE 'HCAPLUS' ENTERED AT 09:39:37 ON 14 MAY 2007
L15            4 S L14 AND (L7 OR L8 OR L9 OR L10)
```

```
=> file hcaplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY   SESSION
FULL ESTIMATED COST                                         0.84      0.84

FILE 'HCAPLUS' ENTERED AT 08:52:21 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907 - 14 May 2007  VOL  ISS  ISS
FILE LAST UPDATED: 13 May 2007  (20070513/ED)
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 14 May 2007  VOL 146 ISS 21
FILE LAST UPDATED: 1 May 2007  (20070501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate

=> s (dose-dense)

        603713 DOSE
        104922 DENSE
L1         147 (DOSE-DENSE)
                 (DOSE(W)DENSE)

=> s cancer

L2      315101 CANCER

=> s tumor

L3      407298 TUMOR

=> s adenocarcinoma

L4       29699 ADENOCARCINOMA

=> s neoplas?

L5      492420 NEOPLAS?

=> s L1 and (L2 or L3 or L4 or L5)

L6         128 L1 AND (L2 OR L3 OR L4 OR L5)

=> s doxorubicin

L7       16483 DOXORUBICIN

=> s cyclophosphamide

L8       18136 CYCLOPHOSPHAMIDE
```

```
=> s paclitaxel

L9       10301 PACLITAXEL

=> s taxane

L10       2878 TAXANE

=> file stnguide

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         2.60       3.44

FILE 'STNGUIDE' ENTERED AT 08:52:32 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 11, 2007 (20070511/UP).

=> file hcaplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.12       3.56

FILE 'HCAPLUS' ENTERED AT 08:53:33 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907 - 14 May 2007  VOL  ISS  ISS
FILE LAST UPDATED: 13 May 2007  (20070513/ED)
held by the publishers listed in the PUBLISHER (PB) field (available
for records published or updated in Chemical Abstracts after December
26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the
the American Chemical Society and is provided to assist you in searching
databases on STN.  Any dissemination, distribution, copying, or storing
of this information, without the prior written consent of CAS, is
strictly prohibited.

FILE COVERS 1907 - 14 May 2007  VOL 146 ISS 21
FILE LAST UPDATED: 1 May 2007  (20070501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate

=> s L6 and L7 and L8 and (L9 or L10)

L11         17 L6 AND L7 AND L8 AND (L9 OR L10)

=> file stnguide

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         2.60       6.16

FILE 'STNGUIDE' ENTERED AT 08:53:34 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE
```

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 11, 2007 (20070511/UP).

=> d l11 1-17 ti
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L11 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Concepts and clinical trials of dose-dense chemotherapy for breast cancer

L11 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Efficacy of pegfilgrastim and darbepoetin alfa as hemotopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy

L11 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Five-year update of an expanded phase II study of dose-dense and -intense doxorubicin, paclitaxel and cyclophosphamide (ATC) in high-risk breast cancer

L11 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Adjuvant Therapy of Breast Cancer

L11 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Evolving treatment approaches for early breast cancer

L11 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741. [Erratum to document cited in CA142:273450]

L11 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose-dense & sequential adjuvant cancer chemotherapy

L11 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741

L11 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose Density in Adjuvant Chemotherapy for Breast Cancer

L11 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose-dense chemotherapy in breast cancer and lymphoma

L11 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI The use of taxanes in early breast cancer

L11 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose-dense treatment prolongs disease-free survival of women with node positive breast cancer

L11 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI A Pilot Study of Dose Intense Doxorubicin and

Cyclophosphamide Followed by Infusional Paclitaxel in High-Risk Primary Breast Cancer

L11 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI The Role of Taxanes in the Adjuvant Treatment of Early Stage Breast Cancer

L11 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Doxorubicin followed by sequential paclitaxel and cyclophosphamide versus concurrent paclitaxel and cyclophosphamide: 5-year results of a Phase II randomized trial of adjuvant dose-dense chemotherapy for women with node-positive breast carcinoma

L11 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI An immunotherapeutic approach to treatment of breast cancer: focus on trastuzumab plus paclitaxel

L11 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Sequential dose-dense doxorubicin, paclitaxel, and cyclophosphamide for resectable high-risk breast cancer: feasibility and efficacy

=> d l11 1 3 6 8 9 9 10 12 13 14 16 17 ti abs bib
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L11 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Concepts and clinical trials of dose-dense chemotherapy for breast cancer
AB This article will review the strategy of dose-dense administration of chemotherapy for breast cancer. Increased dose d. is achieved by reducing the interval between each dose of chemotherapy. The cumulative drug dose remains constant, but the same amount of drug is administered over a shorter period. Math. models of tumor growth have provided the basis for the clin. application of dose-dense chemotherapy. The Norton-Simon model suggests that increasing the dose d. of chemotherapy will increase efficacy by minimizing the opportunity for regrowth of tumor cells between cycles of chemotherapy. Intergroup trial 9741, coordinated by the Cancer and Leukemia Group B (CALGB), tested the 2 hypotheses that dose-dense and sequential administration of chemotherapy regimens incorporating doxorubicin , cyclophosphamide, and paclitaxel would improve disease-free survival and overall survival. A statistically significant 4-yr disease-free survival advantage was detected for the 2 dose -dense regimens compared with the regimens administered every 3 wk. The math. concepts and previous clin. trials of dose d. that contributed to the design of CALGB 9741 will be reviewed. The strengths and limitations of CALGB 9741 will then be discussed before the presentation of future directions of research and recommendations for clin. practice today.
AN 2006:84758 HCAPLUS <<LOGINID::20070514>>
DN 145:20182
TI Concepts and clinical trials of dose-dense chemotherapy for breast cancer
AU Orzano, Jennifer A.; Swain, Sandra M.
CS Cancer Therapeutics Branch, Center for Cancer Research, Department of Health & Human Services, National Cancer Institute, Bethesda, MD, USA
SO Clinical Breast Cancer (2005), 6(5), 402-411
CODEN: CBCLB7; ISSN: 1526-8209
PB CIG Media Group, LP

DT Journal; General Review
LA English
RE.CNT 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Five-year update of an expanded phase II study of dose-dense and -intense doxorubicin, paclitaxel and cyclophosphamide (ATC) in high-risk breast cancer
AB This study evaluated the safety and efficacy of dose-dense and -intense sequential doxorubicin (A), paclitaxel (T) and cyclophosphamide (C) as adjuvant therapy for breast cancer (BC) with ≥4 ipsilateral axillary lymph nodes. Patients were recruited after BC surgery if ≥4 axillary nodes were involved by metastatic cancer. Planned treatment was A 90 mg/m2 three times every 14 days (q14d + 3), T 250 mg/m2 q14d + 3 and C 3 g/m2 q14d + 3 combined with filgrastim support. The study enrolled 85 eligible patients. The median number of lymph nodes involved was 9. Mean dose intensity was >94% of planned for each drug. Common grade 3 toxicities included nausea and/or vomiting (24%), mucositis (18%), neuropathy (16%), palmar-plantar erythrodysesthesia (12%), myalgia (6%) and arthralgia (6%). Grade 3/4 neutropenia occurred in 77 (91%) patients, and 32 (38%) patients had neutropenic fever. One patient developed acute leukemia. Sixty-nine (81%) patients are alive, and 59 (69%) patients are alive and free of distant disease at a median follow-up of 5 years. ATC is a feasible regimen for adjuvant therapy of high-risk BC, with a relatively low rate of relapse at the 5-yr follow up.
AN 2005:1311866 HCAPLUS <<LOGINID::20070514>>
DN 144:343146
TI Five-year update of an expanded phase II study of dose-dense and -intense doxorubicin, paclitaxel and cyclophosphamide (ATC) in high-risk breast cancer
AU Abu-Khalaf, Maysa M.; Windsor, Stephen; Ebisu, Keita; Salikooti, Saritha; Ananthanarayanan, Gowri; Chung, Gina G.; DiGiovanna, Michael P.; Haffty, Bruce G.; Abrams, Martin; Farber, Leonard R.; Hsu, Arlene D.; Reiss, Michael; Zelterman, Daniel; Burtness, Barbara A.
CS Jersey Shore University Medical Center, Neptune, NJ, USA
SO Oncology (2005), 69(5), 372-383
CODEN: ONCOBS; ISSN: 0030-2414
PB S. Karger AG
DT Journal
LA English
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741. [Erratum to document cited in CA142:273450]
AB The corrected version of Table 6 is given.
AN 2005:279234 HCAPLUS <<LOGINID::20070514>>
DN 142:309436
TI Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741. [Erratum to document cited in CA142:273450]
AU Citron, Marc L.; Berry, Donald A.; Cirrincione, Constance; Hudis, Clifford; Winer, Eric P.; Gradishar, William J.; Davidson, Nancy E.;

Martino, Silvana; Livingston, Robert; Ingle, James N.; Perez, Edith A.; Carpenter, John; Jurd, David; Solland, James F.; Smith, Barbara L.; Sartor, Carolyn I.; Leung, Eleanor H.; Abrams, Jeffrey; Schilsky, Richard L.; Muss, Hyman B.; Norton, Larry

CS ProHEALTH Care Associates, LLP, Lake Success, NY, USA

SO Journal of Clinical Oncology (2003), 21(11), 2226
CODEN: JCONDN; ISSN: 0732-183X

PB American Society of Clinical Oncology

DT Journal

LA English

L11 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN

TI Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741

AB Using a 2 + 2 factorial design, we studied the adjuvant chemotherapy of women with axillary node-pos. breast cancer to compare sequential doxorubicin (A), paclitaxel (T), and cyclophosphamide (C) with concurrent doxorubicin and cyclophosphamide (AC) followed by paclitaxel (T) for disease-free (DFS) and overall survival (OS); to determine whether the dose d. of the agents improves DFS and OS; and to compare toxicities. A total of 2,005 female patients were randomly assigned to receive one of the following regimens: (I) sequential A + 4 (doses) → T + 4 → C + 4 with doses every 3 wk, (II) sequential A + 4 → T + 4 → C + 4 every 2 wk with filgrastim, (III) concurrent AC + 4 → T + 4 every 3 wk, or (IV) concurrent AC + 4 → T + 4 every 2 wk with filgrastim. A protocol-specified anal. was performed at a median follow-up of 36 mo: 315 patients had experienced relapse or died, compared with 515 expected treatment failures. Dose-dense treatment improved the primary end point, DFS (risk ratio [RR] = 0.74; P = .010), and OS (RR = 0.69; P = .013). Four-year DFS was 82% for the dose-dense regimens and 75% for the others. There was no difference in either DFS or OS between the concurrent and sequential schedules. There was no interaction between d. and sequence. Severe neutropenia was less frequent in patients who received the dose-dense regimens. Dose d. improves clin. outcomes significantly, despite the lower than expected number of events at this time. Sequential chemotherapy is as effective as concurrent chemotherapy.

AN 2004:934715 HCAPLUS <<LOGINID::20070514>>

DN 142:273450

TI Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group B trial 9741

AU Citron, Marc L.; Berry, Donald A.; Cirrincione, Constance; Hudis, Clifford; Winer, Eric P.; Gradishar, William J.; Davidson, Nancy E.; Martino, Silvana; Livingston, Robert; Ingle, James N.; Perez, Edith A.; Carpenter, John; Hurd, David; Holland, James F.; Smith, Barbara L.; Sartor, Carolyn I.; Leung, Eleanor H.; Abrams, Jeffrey; Schilsky, Richard L.; Muss, Hyman B.; Norton, Larry

CS ProHEALTH Care Associates, LLP, Lake Success, NY, USA

SO Journal of Clinical Oncology (2003), 21(8), 1431-1439
CODEN: JCONDN; ISSN: 0732-183X

PB American Society of Clinical Oncology

DT Journal

LA English

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose Density in Adjuvant Chemotherapy for Breast Cancer
AB A review. BACKGROUND: Dose-dense chemotherapy increases the dose intensity of the regimen by delivering standard-dose chemotherapy with shorter intervals between the cycles. This article discusses the rationale for dose-dense therapy and reviews the results with dose-dense adjuvant regimens in recent clin. trials in breast cancer. METHODS: The papers for this review covered evidence of a dose-response relation in cancer chemotherapy; the rationale for dose-intense (and specifically dose-dense) therapy; and clin. experience with dose-dense regimens in adjuvant chemotherapy for breast cancer, with particular attention to outcomes and toxicity. RESULTS: Evidence supports maintaining the dose intensity of adjuvant chemotherapy within the conventional dose range. Disease-free and overall survival with combination cyclophosphamide, methotrexate, and fluorouracil are significantly improved when patients receive within 85% of the planned dose. Moderate and high dose cyclophosphamide, doxorubicin, and fluorouracil within the standard range results in greater disease-free and overall survival than the low dose regimen. The sequential addition of paclitaxel after concurrent doxorubicin and cyclophosphamide also significantly improves survival. Disease-free and overall survival with dose-dense sequential or concurrent doxorubicin , cyclophosphamide, and paclitaxel with filgrastim (rhG-CSF; NEUPOGEN) support are significantly greater than with conventional schedules (q21d). CONCLUSIONS: The delivered dose intensity of adjuvant chemotherapy within the standard dose range is an important predictor of the clin. outcome. Prospective trials of high-dose chemotherapy have shown no improvement over standard regimens, and toxicity was greater. Dose-dense adjuvant chemotherapy improves the clin. outcomes with doxorubicin-containing regimens. Filgrastim support enables the delivery of dose-dense chemotherapy and reduces the risk of neutropenia and its complications.
AN 2004:803733 HCAPLUS <<LOGINID::20070514>>
DN 142:168570
TI Dose Density in Adjuvant Chemotherapy for Breast Cancer
AU Citron, Marc L.
CS Albert Einstein College of Medicine, Bronx, NY, USA
SO Cancer Investigation (2004), 22(4), 555-568
CODEN: CINVD7; ISSN: 0735-7907
PB Marcel Dekker, Inc.
DT Journal; General Review
LA English
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose Density in Adjuvant Chemotherapy for Breast Cancer
AB A review. BACKGROUND: Dose-dense chemotherapy increases the dose intensity of the regimen by delivering standard-dose chemotherapy with shorter intervals between the cycles. This article discusses the rationale for dose-dense therapy and reviews the results with dose-dense adjuvant regimens in recent clin. trials in breast cancer. METHODS: The papers for this review covered evidence of a dose-response relation in cancer chemotherapy; the rationale for dose-intense (and specifically dose-dense) therapy; and clin. experience with dose-dense regimens in adjuvant chemotherapy for breast cancer, with particular attention to outcomes and toxicity. RESULTS: Evidence supports maintaining the dose intensity of adjuvant chemotherapy within the conventional dose range. Disease-free and overall survival with combination cyclophosphamide, methotrexate, and fluorouracil are significantly improved when patients

receive within 85% of the planned dose. Moderate and high dose cyclophosphamide, doxorubicin, and fluorouracil within the standard range results in greater disease-free and overall survival than the low dose regimen. The sequential addition of paclitaxel after concurrent doxorubicin and cyclophosphamide also significantly improves survival. Disease-free and overall survival with dose-dense sequential or concurrent doxorubicin , cyclophosphamide, and paclitaxel with filgrastim (rhG-CSF; NEUPOGEN) support are significantly greater than with conventional schedules (q21d). CONCLUSIONS: The delivered dose intensity of adjuvant chemotherapy within the standard dose range is an important predictor of the clin. outcome. Prospective trials of high-dose chemotherapy have shown no improvement over standard regimens, and toxicity was greater. Dose-dense adjuvant chemotherapy improves the clin. outcomes with doxorubicin-containing regimens. Filgrastim support enables the delivery of dose-dense chemotherapy and reduces the risk of neutropenia and its complications.

AN 2004:803733 HCAPLUS <<LOGINID::20070514>>
DN 142:168570
TI Dose Density in Adjuvant Chemotherapy for Breast Cancer
AU Citron, Marc L.
CS Albert Einstein College of Medicine, Bronx, NY, USA
SO Cancer Investigation (2004), 22(4), 555-568
CODEN: CINVD7; ISSN: 0735-7907
PB Marcel Dekker, Inc.
DT Journal; General Review
LA English
RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose-dense chemotherapy in breast cancer and lymphoma
AB A review. Adjuvant combination chemotherapy reduces the risk of relapse and death for patients with invasive breast cancer and adds to the benefits obtained with hormonal treatment. Generally, anthracycline-containing regimens are superior to non-anthracycline regimens, treatments longer than 6 mo are not advantageous and high-dose chemotherapy regimens, which require autologous hematopoietic stem cell support, have not proved consistently superior. The development and evaluation of the taxanes was highly anticipated as they have shown high levels of efficacy while appearing to be non-cross-resistant with partially non-overlapping toxicities. A role for taxanes in the adjuvant or neoadjuvant setting is now widely acknowledged, although they are not currently approved for treatment of early breast cancer in Europe. In patients with aggressive lymphoma who receive cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy, 40% to 70% of patients attain a complete remission, depending on risk factors such as age and extranodal involvement. Second- and third-generation regimens like m-BACOD (methotrexate, bleomycin, cyclophosphamide, etoposide), Pro-MACE-CytaBOM (prednisone, methotrexate, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate), and MACOP-B (methotrexate with leucovorin rescue, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin) have largely failed to improve treatment outcome. The use of monoclonal anti-CD20 antibodies or dose escalation have shown promising results in improving relapse-free and survival rates. In patients with breast cancer, the key Cancer and Leukemia Group B 9741 trial showed that dose-dense doxorubicin , cyclophosphamide, and paclitaxel chemotherapy with granulocyte colony-stimulating factor (G-CSF), repeated every 2 wk, is superior to the same regimen administered at standard 3-weekly intervals. In lymphoma, dose-dense CHOP chemotherapy has shown

superiority over standard CHOP regimens, particularly in elderly patients with aggressive non-Hodgkin's lymphoma. G-CSF factor is essential to enable the administration of dose-dense chemotherapy and any reduction in its use leads to significant increases in infectious complications. Current evidence suggests that dose-dense chemotherapy, enabled by G-CSF, is an important breakthrough in the evolution of chemotherapy for breast cancer and lymphoma.

AN 2004:567671 HCAPLUS <<LOGINID::20070514>>
DN 141:150362
TI Dose-dense chemotherapy in breast cancer and lymphoma
AU Hudis, Clifford A.; Schmitz, Norbert
CS Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
SO Seminars in Oncology (2004), 31(3, Suppl. 8), 19-26
CODEN: SOLGAV; ISSN: 0093-7754
PB Elsevier Inc.
DT Journal; General Review
LA English
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Dose-dense treatment prolongs disease-free survival of women with node positive breast cancer
AB A review and discussion. The impact of dose d. and drug sequence (concurrent vs. sequential) in women with axillary node-pos. primary breast cancer was assessed. Breast cancer is the second leading cause of cancer mortality in women. The prognosis for patients with extensive axillary lymph nodes involvement is poor. Important trial demonstrated that shortening the time interval between each chemotherapy cycle while maintaining the same dose size resulted in a significant improvement in disease-free and overall survival in patients with node-pos. breast cancer without increase in toxicity. A dose-dense treatment regimen significantly improved clin. outcomes in women with axillary node-pos. primary breast cancer. Concurrent chemotherapy is proved to be as effective as sequential chemotherapy.
AN 2003:705588 HCAPLUS <<LOGINID::20070514>>
DN 140:263316
TI Dose-dense treatment prolongs disease-free survival of women with node positive breast cancer
AU Dang, Chau; Seidman, Andrew D.
CS Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
SO Cancer Treatment Reviews (2003), 29(5), 453-456
CODEN: CTREDJ; ISSN: 0305-7372
PB Elsevier Science Ltd.
DT Journal; General Review
LA English
RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI A Pilot Study of Dose Intense Doxorubicin and Cyclophosphamide Followed by Infusional Paclitaxel in High-Risk Primary Breast Cancer
AB We conducted a pilot study of dose dense doxorubicin and cyclophosphamide (AC) combination chemotherapy followed by infusional paclitaxel (T) in primary breast cancer to determine its safety and feasibility. Twenty-two subjects (10 with stage II and ≥4 pos. lymph nodes, and 12 with stage III disease) were treated with AC (A 60 mg/m2 and C 2000 mg/m2) with filgrastim every 14 days for three cycles followed by infusional

paclitaxel (140 mg/m2 over 96 h) every 14 days for three cycles. Mean overall cycle length was 15.3 days and mean duration of therapy was 92 days. Dose redns. of C or T were required in 7/132 (5.3%) cycles for mucositis, diarrhea, or failure to recover platelets by day 15. Ninety-five percent of subjects had grade 4 neutropenia and 1 subject had a platelet nadir of <20,000. Actual delivered dose intensity (DI) over six cycles was: A 27 mg/m2 per wk; C 892 mg/m2 per wk; T 64 mg/m2 per wk (90.6, 89.2, and 91.4% of planned DI, resp.). Average total dose administered was: A 180 mg/m2; C 5880 mg/m2; T 403 mg/m2 (100, 98, and 96% of planned total doses, resp.). Clin. response rate in 10 subjects receiving neoadjuvant therapy was 100% (4 complete response, 6 partial response). Four subjects had a pathol. complete response (three subjects without evidence of malignancy and one subject with ductal carcinoma in situ.). Administration of dose dense AC followed by infusional paclitaxel in 14-day cycles is feasible and this regimen is active in breast cancer.

AN 2003:665006 HCAPLUS <<LOGINID::20070514>>
DN 140:174554
TI A Pilot Study of Dose Intense Doxorubicin and Cyclophosphamide Followed by Infusional Paclitaxel in High-Risk Primary Breast Cancer
AU Zujewski, Jo Anne; Eng-Wong, Jennifer; O'Shaughnessy, Joyce; Venzon, David; Chow, Catherine; Danforth, David; Kohler, David R.; Cusack, Georgia; Riseberg, David; Cowan, Kenneth H.
CS National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
SO Breast Cancer Research and Treatment (2003), 81(1), 41-51
CODEN: BCTRD6; ISSN: 0167-6806
PB Kluwer Academic Publishers
DT Journal
LA English
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI The Role of Taxanes in the Adjuvant Treatment of Early Stage Breast Cancer
AB A review. Adjuvant chemotherapy plays a significant incremental role in improving survival in patients with early stage breast cancer. Survival benefits gained in the adjuvant setting with anthracycline-based polychemotherapy regimens are now level-1 evidence based, and in an attempt to further these gains, many randomized trials are examining new treatment options. Other important goals include defining the magnitude of benefit with current and investigational regimens in prospectively defined risk groups. The taxanes, docetaxel and paclitaxel, are under investigation in the adjuvant setting in a large series of randomized clin. trials that will enroll not less than 56,000 women, among whom 22,000 women will contribute to paclitaxel-related questions and 34,000 to docetaxel-related questions. The main focus of this review will be the first-generation trials, which include at least one non-taxane arm. For the most part, trials with paclitaxel have evaluated the agent in sequence with anthracycline-based therapy, while trials with docetaxel are evaluating it as an alternative to one of the standard drugs in a combination regimen as well as in sequence with anthracycline-based regimens. To date, results from four randomized trials with adjuvant paclitaxel and two with docetaxel have been presented. All reports but one are based on interim analyses. Only one of the paclitaxel trials so far demonstrated a statistically significant improvement in disease-free and overall survival relative to the comparator, while a second trial demonstrated superiority of dose-dense chemotherapy over conventional dosing. Interim results with docetaxel suggest that substituting docetaxel for fluorouracil in combination with doxorubicin and cyclophosphamide results in improved

disease-free survival, with a trend toward improved overall survival. Completion of ongoing trials and maturation of the current data will further define the role of taxanes in the adjuvant treatment of early stage breast cancer.

AN 2003:464401 HCAPLUS <<LOGINID::20070514>>
DN 140:22469
TI The Role of Taxanes in the Adjuvant Treatment of Early Stage Breast Cancer
AU Piccart, Martine
CS Jules Bordet Institute, Brussels, Belg.
SO Breast Cancer Research and Treatment (2003), 79(Suppl. 1), S25-S34
CODEN: BCTRD6; ISSN: 0167-6806
PB Kluwer Academic Publishers
DT Journal; General Review
LA English
RE.CNT 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI An immunotherapeutic approach to treatment of breast cancer: focus on trastuzumab plus paclitaxel
AB A review, with 22 refs. Recent emphasis has focused on the development of an immunotherapeutic approach toward the treatment of breast cancer. In particular, evaluation of antibodies and vaccines are active areas of research. The monoclonal antibody trastuzumab (H), directed against the HER-2/neu protein, has resulted in inhibition of tumor growth in both preclin. and clin. studies. This effect can be increased when used in combination with several chemotherapeutic agents. A randomized trial of chemotherapy alone vs. chemotherapy plus H in untreated metastatic breast cancer patients found prolonged survival in the combination therapy arm. Cardiac toxicity was increased with doxorubicin and cyclophosphamide plus H but not for paclitaxel (T) plus H. Several trials of dose-dense weekly T have found minimal toxicity and significant clin. benefit. These findings prompted the initiation of a trial to evaluate weekly 1-h T plus weekly H. Preliminary data from this ongoing study demonstrate few side effects and a response rate of 64% (95%CI 42-76%). The optimal role of H in the treatment of breast cancer has not yet been defined. Addnl. evaluation in the metastatic and adjuvant settings is planned.
AN 2000:467710 HCAPLUS <<LOGINID::20070514>>
DN 134:94947
TI An immunotherapeutic approach to treatment of breast cancer: focus on trastuzumab plus paclitaxel
AU Gilewski, Teresa; Seidman, Andrew; Norton, Larry; Hudis, Clifford
CS Memorial Sloan-Kettering Cancer Center, New York, NY, NY10021, USA
SO Cancer Chemotherapy and Pharmacology (2000), 46(Suppl.), S23-S26
CODEN: CCPHDZ; ISSN: 0344-5704
PB Springer-Verlag
DT Journal; General Review
LA English
RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Sequential dose-dense doxorubicin, paclitaxel, and cyclophosphamide for resectable high-risk breast cancer: feasibility and efficacy
AB Dose-dense chemotherapy is predicted to be a superior treatment plan. Therefore, we studied dose-dense doxorubicin, paclitaxel, and cyclophosphamide (A → T → C) as adjuvant therapy. Patients with resected breast cancer involving four or more ipsilateral axillary lymph nodes were treated with nine cycles of chemotherapy, using 14-day

intertreatment intervals. Doses were as follows: doxorubicin 90 mg/m2 + 3, then paclitaxel 250 mg/m2/24 h + 3, and then cyclophosphamide 3.0 g/m2 + 3; all doses were given with s.c. injections of 5 μg/kg granulocyte colony-stimulating factor on days 3 through 10. Amenorrheic patients with hormone receptor-pos. tumors received tamoxifen 20 mg/day for 5 yr. Patients treated with breast conservation, those with 10 or more pos. nodes, and those with tumors larger than 5 cm received radiotherapy. Between Mar. 1993 and June 1994, we enrolled 42 patients. The median age was 46 yr (range, 29 to 63 yr), the median number of pos. lymph nodes was eight (range, four to 25), and the median tumor size was 3.0 cm (range, 0 to 11.0 cm). The median intertreatment interval was 14 days (range, 13 to 36 days), and the median delivered dose-intensity exceeded 92% of the planned dose-intensity for all three drugs. Hospital admission was required for 29 patients (69%), and 28 patients (67%) required blood product transfusion. No treatment-related deaths or cardiac toxicities occurred. Doxorubicin was dose-reduced in four patients (10%) and paclitaxel was reduced in eight (20%). At a median follow-up from surgery of 48 mo (range, 3 to 57 mo), nine patients (19%) had relapsed, the actuarial disease-free survival rate was 78% (95% confidence interval, 66% to 92%), and four patients (10%) had died of metastatic disease. Dose-dense sequential adjuvant chemotherapy with doxorubicin, paclitaxel, and cyclophosphamide (A → T → C) is feasible and promising. Several ongoing phase III trials are evaluating this approach.

AN 1999:50879 HCAPLUS <<LOGINID::20070514>>
DN 130:232080
TI Sequential dose-dense doxorubicin, paclitaxel, and cyclophosphamide for resectable high-risk breast cancer: feasibility and efficacy
AU Hudis, C.; Seidman, A.; Baselga, J.; Raptis, G.; Lebwohl, D.; Gilewski, T.; Moynahan, M.; Sklarin, N.; Fennelly, D.; Crown, J. P. A.; Surbone, A.; Uhlenhopp, M.; Riedel, E.; Yao, T. J.; Norton, L.
CS Breast and Gynecologic Cancer Medicine Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 10024, USA
SO Journal of Clinical Oncology (1999), 17(1), 93-100
CODEN: JCONDN; ISSN: 0732-183X
PB Lippincott Williams & Wilkins
DT Journal
LA English
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 08:50:10 ON 14 MAY 2007)

FILE 'HCAPLUS' ENTERED AT 08:52:21 ON 14 MAY 2007
L1 147 S (DOSE-DENSE)
L2 315101 S CANCER
L3 407298 S TUMOR
L4 29699 S ADENOCARCINOMA
L5 492420 S NEOPLAS?
L6 128 S L1 AND (L2 OR L3 OR L4 OR L5)
L7 16483 S DOXORUBICIN
L8 18136 S CYCLOPHOSPHAMIDE
L9 10301 S PACLITAXEL
L10 2878 S TAXANE

FILE 'STNGUIDE' ENTERED AT 08:52:32 ON 14 MAY 2007

FILE 'HCAPLUS' ENTERED AT 08:53:33 ON 14 MAY 2007
L11 17 S L6 AND L7 AND L8 AND (L9 OR L10)

FILE 'STNGUIDE' ENTERED AT 08:53:34 ON 14 MAY 2007

FILE 'HCAPLUS' ENTERED AT 08:53:58 ON 14 MAY 2007

FILE 'STNGUIDE' ENTERED AT 08:53:59 ON 14 MAY 2007

FILE 'HCAPLUS' ENTERED AT 08:54:50 ON 14 MAY 2007

FILE 'STNGUIDE' ENTERED AT 08:54:51 ON 14 MAY 2007

=> log hold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	51.28

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 08:55:03 ON 14 MAY 2007

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSPTAEXO1623

PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'STNGUIDE' AT 09:37:09 ON 14 MAY 2007
FILE 'STNGUIDE' ENTERED AT 09:37:09 ON 14 MAY 2007
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHEs

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	51.28

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.12	51.34

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

FILE 'HCAPLUS' ENTERED AT 09:38:21 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907 - 14 May 2007 VOL ISS ISS
FILE LAST UPDATED: 13 May 2007 (20070513/ED)
held by the publishers listed in the PUBLISHER (PB) field (available

for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 14 May 2007 VOL 146 ISS 21
FILE LAST UPDATED: 1 May 2007 (20070501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate

=> s (dose-escalation) or (dose-intens?)

```
        603713 DOSE
          2683 ESCALATION
          2010 DOSE-ESCALATION
                 (DOSE(W)ESCALATION)
        603713 DOSE
        724086 INTENS?
          1442 DOSE-INTENS?
                 (DOSE(W)INTENS?)
L12       3385 (DOSE-ESCALATION) OR (DOSE-INTENS?)
```

=> s L12 and (L2 and L3 and L4 and L5 and L6 and L7 and L8 and (L9 or L10))

```
L13          0 L12 AND (L2 AND L3 AND L4 AND L5 AND L6 AND L7 AND L8 AND (L9
              OR L10))
```

=> file stnguide

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.60	53.94

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

FILE 'STNGUIDE' ENTERED AT 09:38:24 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 11, 2007 (20070511/UP).

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	54.00

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

FILE 'HCAPLUS' ENTERED AT 09:38:58 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907 - 14 May 2007 VOL ISS ISS
FILE LAST UPDATED: 13 May 2007 (20070513/ED)
held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 14 May 2007 VOL 146 ISS 21
FILE LAST UPDATED: 1 May 2007 (20070501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate

=> s L12 and (L2 and L3 and L4 and L5)

L14 27 L12 AND (L2 AND L3 AND L4 AND L5)

=> file stnguide

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.60	56.60

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

FILE 'STNGUIDE' ENTERED AT 09:38:59 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 11, 2007 (20070511/UP).

=> file hcaplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.06	56.66

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

FILE 'HCAPLUS' ENTERED AT 09:39:37 ON 14 MAY 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE COVERS 1907 - 14 May 2007 VOL ISS ISS
FILE LAST UPDATED: 13 May 2007 (20070513/ED)
held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications.
The CA Lexicon is the copyrighted intellectual property of the the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 14 May 2007 VOL 146 ISS 21
FILE LAST UPDATED: 1 May 2007 (20070501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate

=> s L14 and (L7 or L8 or L9 or L10)

L15 4 L14 AND (L7 OR L8 OR L9 OR L10)

=> file stnguide

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.60	59.26

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.36

FILE 'STNGUIDE' ENTERED AT 09:39:38 ON 14 MAY 2007

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: May 11, 2007 (20070511/UP).

=> d l15 1-4 ti abs bib
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

L15 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Phase I Study of the Taxane BMS-188797 in Combination with Carboplatin Administered Every 3 Weeks in Patients with Solid Malignancies
AB Rationale: BMS-188797 is one of several novel taxanes in ongoing clin. development. It has superior activity in exptl. tumor models when compared with paclitaxel. BMS-188797 has a single C-4 modification, a 4-desacetyl-4-methylcarbonate, compared with paclitaxel. Methods: We did a phase I study, in which a fixed dose of carboplatin was combined with a dose escalation schedule of BMS-188797, both administered once every 3 wk, in patients with advanced solid malignancies. Results: Thirty patients were treated, 11 at the proposed recommended phase II dose. The dose-limiting toxicity was myelosuppression. There was a linear relationship between administered dose of BMS-188797 and the measured area under the curve (AUC). There was significant interpatient variability of BMS-188797 AUC at the maximum tolerated dose. Two radiog. partial responses were observed: one patient with duodenal adenocarcinoma and one patient with esophageal adenocarcinoma (time on study, 19 and 30 wk, resp.). Conclusion: The recommended phase II dose for BMS-188797 and carboplatin administered on a once-every-3 wk schedule is carboplatin AUC = 5 mg min/mL and BMS-188797 at a dose of 135 mg/m2.
AN 2006:63621 HCAPLUS <<LOGINID::20070514>>
DN 145:55469
TI Phase I Study of the Taxane BMS-188797 in Combination with Carboplatin Administered Every 3 Weeks in Patients with Solid Malignancies
AU Fishman, Mayer N.; Garrett, Christopher R.; Simon, George R.; Chiappori, Alberto A.; Lush, Richard M.; Dinwoodie, William R.; Mahany, J. Joseph; Dellaportas, Anne M.; Cantor, Alan; Gollerki, Ashwin; Cohen, Marvin B.;

Sullivan, Daniel M.
CS Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, 33612, USA
SO Clinical Cancer Research (2006), 12(2), 523-528
CODEN: CCREF4; ISSN: 1078-0432
PB American Association for Cancer Research
DT Journal
LA English
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN
TI Phase I Study of Oral CI-994 in Combination with Carboplatin and Paclitaxel in the Treatment of Patients with Advanced Solid Tumors
AB PURPOSE: To determine maximum tolerated dose of CI-994, a novel oral histone deacetylase inhibitor, in combination with carboplatin and paclitaxel in patients with advanced solid tumors. Patients and METHODS: Patients with advanced solid tumors who had received two or fewer prior chemotherapy regimens were eligible for trial. Five cohorts of patients were treated with escalating doses (4-6 mg/m2) and alternative schedules (7 days or 14 days) of CI-994. Dose escalation of paclitaxel was performed to achieve tolerability of CI-994 with a paclitaxel dose of 225 mg/m2 when administered in combination with carboplatin. Pharmacokinetic assessment of CI-994 was performed by using liquid chromatog./mass spectrometry. Histone deacetylation inhibition was determined by Western blot anal. RESULTS: A total of 30 patients (median age 58 years) were entered into five treatment cohorts. Maximum tolerated dose of CI-994 was determined to be 4 mg/m2 administered for 7 consecutive days following paclitaxel at a dose of 225 mg/m2 and carboplatin at an area under the curve (AUC) of 6 every 21 days. Neutropenia, thrombocytopenia, and grade 3 respiratory insufficiency limited further dose escalation of CI-994. Pharmacokinetics showed that CI-994 absorption and disposition were unaffected by carboplatin and paclitaxel coadministration. Association between histone H3 acetylation levels and disease response was suggested. A subset of patients with lymphocyte H3 acetylation levels at least 1.5-fold times baseline all achieved either a clin. response or stable disease. All evaluable patients with progressive disease (PD) had H3 acetylation levels < 1.5-fold times baseline. Twenty-four of the 30 patients received greater than one cycle of treatment. Five of these patients achieved a partial response (3 nonsmall cell lung cancer , 1 colorectal cancer, and 1 unknown primary) and 2 patients achieved a complete response (esophageal and bladder cancer). CONCLUSION: The combination of CI-994 at a dose of 4 mg/m2 administered orally for 7 consecutive days can be safely coadministered with paclitaxel at a dose of 225 mg/m2 and carboplatin at an AUC of 6 on day 1 of a 21-day cycle. Evidence of antitumor activity is suggested and may correlate with histone modulation.
AN 2004:1034487 HCAPLUS <<LOGINID::20070514>>
DN 142:253948
TI Phase I Study of Oral CI-994 in Combination with Carboplatin and Paclitaxel in the Treatment of Patients with Advanced Solid Tumors
AU Pauer, Lynne R.; Olivares, Jairo; Cunningham, Casey; Williams, Adrienne; Grove, William; Kraker, Alan; Olson, Stephen; Nemunaitis, John
CS Pfizer Global Research and Development, Ann Arbor, MI, USA
SO Cancer Investigation (2004), 22(6), 886-896
CODEN: CINVD7; ISSN: 0735-7907
PB Taylor & Francis, Inc.
DT Journal
LA English
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN

TI Chemotherapy response of breast cancer depends on HER-2 status and anthracycline dose intensity in the neoadjuvant setting

AB We evaluated the predictive value of a tumor's HER-2 status for chemotherapy response in the neoadjuvant setting and the effect of anthracycline dose intensity on this predictive value. HER-2 status was evaluated by immunochem. on microbiopsy before neoadjuvant chemotherapy (monoclonal antibody CB-11; Novocastra) in 39 patients (group A) treated with FEC50 (500 mg/m2 5-fluorouracil, 50 mg/m2 epirubicin, and 500 mg/m2 cyclophosphamide) and 40 patients (group B) treated with FEC100 (500 mg/m2 5-fluorouracil, 100 mg/m2 epirubicin, and 500 mg/m2 cyclophosphamide). All tumors were stage II or noninflammatory stage III adenocarcinoma. Overall response rate (OR) was evaluated through ultrasound and mammog. measurements. Pathol. complete response was evaluated by tumor excision and axillary node resection after six cycles of chemotherapy. Patient and tumor characteristics (age, tumor size, clin. nodal status, SBR grade, hormonal receptor status, and HER-2 expression) were similar in the two groups. In univariate analyses, anthracycline dose was the only factor predictive of response (OR = 61.5% with FEC50; OR = 82.5% with FEC100; P = 0.038). When anthracycline dose was correlated with HER-2 status, an OR of 73.9% was demonstrated in HER-2- tumors (tumors without HER-2 overexpression), and an OR of 12.5% was demonstrated in HER-2+ tumors (tumors with HER-2 with overexpression) in group A. In group B, an OR of 69.5% was demonstrated in HER-2- tumors, and an OR of 100% was demonstrated in HER-2+ tumors. There was no difference in OR for HER-2- tumors treated with FEC50 or FEC100 (P = 0.74). On the other hand, erbB-2+ tumors treated with FEC100 had a significantly better OR than HER-2+ tumors treated with FEC50 (P = 0.0003). In a multivariate anal., the most powerful predictive factor of OR was a conditional variable associating anthracycline dose with HER-2 status. Low-dose anthracycline and HER-2+ predicted a poor OR, low- or high-dose anthracycline and HER-2- predicted an intermediate OR, and high-dose anthracycline and HER-2+ predicted a high OR. Our results merit addnl. studies, given the possibility for choosing anthracycline dose according to a tumor's HER-2 status.

AN 2001:509202 HCAPLUS <<LOGINID::20070514>>

DN 135:298313

TI Chemotherapy response of breast cancer depends on HER-2 status and anthracycline dose intensity in the neoadjuvant setting

AU Petit, Thierry; Borel, Christian; Ghnassia, Jean-Pierre; Rodier, Jean-Francois; Escande, Anne; Mors, Ricardo; Haegele, Pierre

CS Departments of Medical Oncology, Strasbourg, 67085, Fr.

SO Clinical Cancer Research (2001), 7(6), 1577-1581
CODEN: CCREF4; ISSN: 1078-0432

PB American Association for Cancer Research

DT Journal

LA English

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2007 ACS on STN

TI Expression and function of β-glucuronidase in pancreatic cancer: potential role in drug targeting

AB Improvement of non-surgical strategies is a pivotal task in the treatment of pancreatic cancer. Response to treatment with most anticancer agents has been very poor, probably due to insufficient drug concentration in tumor tissue. Increased response rates during chemotherapy might be achieved by dose escalation; however, this approach is often hampered by severe side effects. One strategy to overcome these adverse effects is application of nontoxic glucuronide prodrugs from which the active moiety is released by β-glucuronidase within or near the tumor. The use of

glucuronide prodrugs in pancreatic cancer requires increased expression of the enzyme in the diseased tissue, a problem that has not been addressed so far. We therefore investigated function and expression of β-glucuronidase in tissue samples from human healthy pancreas (n=7) and pancreatic adenocarcinoma (n=8), resp. Comparing the ability of tissue homogenates to cleave the standard substrate 4-methylumbelliferyl-β-D-glucuronide, we found a significantly increased specific β-glucuronidase activity in pancreatic cancer (median: 133; 75% percentile: 286; 25% percentile: 111 nmol/mg per h) as compared to healthy pancreas (median: 74; 75% percentile: 113; 25% percentile: 71 nmol/mg per h). Enzyme kinetic expts. with the model prodrug N-[4-β-glucuronyl-3-nitrobenzyloxycarbonyl] doxorubicin (HMR 1826) demonstrated bioactivation of HMR 1826 by pancreatic β-glucuronidase. Enzymic activity was found to be closely related to enzyme contents (r=0.87) as assessed by Western blot anal. Our data indicate that increased β-glucuronidase activity in pancreatic cancer seems to be due to an elevated steady-state level of the protein. This may be the basis for new therapeutic strategies in treatment of pancreatic carcinoma by using glucuronide prodrugs of anticancer agents.

AN 2000:627198 HCAPLUS <<LOGINID::20070514>>
DN 133:271539
TI Expression and function of β-glucuronidase in pancreatic cancer: potential role in drug targeting
AU Sperker, Bernhard; Werner, Ulrike; Murdter, Thomas E.; Tekkaya, Ceren; Fritz, Peter; Wacke, Rainer; Adam, Ulrich; Gerken, Manfred; Drewelow, Bernd; Kroemer, Heyo K.
CS Ernst-Moritz-Arndt-Universitat Greifswald, Institut fur Pharmakologie, Greifswald, D-17487, Germany
SO Naunyn-Schmiedeberg's Archives of Pharmacology (2000), 362(2), 110-115
CODEN: NSAPCC; ISSN: 0028-1298
PB Springer-Verlag
DT Journal
LA English
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

CALGB 9344 Presented at ASCO

The following abstract for CALGB 9344: Doxorubicin dose escalation, with or without Taxol, as part of the CA adjuvant chemo regimen for node-positive breast cancer: A Phase III Intergroup Study, *was presented at the American Society of Clinical Oncology, May 18, 1998. (Proc ASCO 17:390a, 1998)*

Improved disease-free and overall survival from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients with node-positive primary breast cancer.

I.C. Henderson, D. Berry, G. Demetri, C. Cirrincione, L. Goldstein, S. Martino, J.N. Ingle, M.R. Cooper, G. Canellos, E. Borden, G. Fleming, J.F. Holland, S. Graziano, J. Carpenter, H. Muss, L. Norton., For CALGB, ECOG, SWOG, and NCCTG.

No previous randomized trial has found an adjuvant chemotherapy more active than doxorubicin plus cyclophosphamide (C). To test if dose escalation of doxorubicin, or the sequential use of paclitaxel (as suggested by modelling) could improve results, 3170 patients were randomized between May 1, 1994 and April 15, 1997 in a 3 x 2 factorial trial design to cyclophosphamide, 600 mg/m^2 plus doxorubicin 60, 75, or 90 mg/m^2 (+ G-CSF) q 3 wks x 4 followed either by no paclitaxel (AC) or by paclitaxel 175 mg/m^2 q 3 wks x 4 (AC→T). Tamoxifen 20 mg po daily for 5 years was then offered to patients with estrogen receptor positive tumors (ER+). An independent board provided group sequential monitoring. The arms were balanced in entry characteristics: 62% were premenopausal and 58% were ER+; 46% had 1-3 involved axillary nodes, 42% had 4 to 9, and 12% had 10 or more. At the first pre-planned interim analysis (450 events), no differences in disease-free survival or overall survival related to doxorubicin dose were seen, but use of paclitaxel reduced the recurrence rate by 22% and the death rate by 26% by multivariate analysis.

Kaplan-Meier estimates at 18 months
(p unadjusted for interim analysis):

	AC	AC →T	p =
Disease-Free	86% ± 1.2%	90% ± 1.0%	0.0077
Overall Survival	95% ± 0.7%	97% ± 0.6%	0.0390

No unusual toxicities of doxorubicin plus cyclophosphamide were seen. Common toxicities (grade ≥ 3) in patients given paclitaxel were: transient myclosuppression 21%, neuropathy 5%, pain 5%, and hyperglycemia 5%. Post-chemotherapy cardiotoxicity occurred in 6% of patients but was not significantly associated with the dose levels of doxorubicin or the use of paclitaxel. Hence, evidence to date indicates that the sequential addition of paclitaxel to doxorubicin plus cyclophosphamide as postoperative adjuvant therapy of node-positive primary breast cancer is well tolerated and significantly improves disease-free survival and overall survival.

CALGB Study Funding

Support is available to qualifying institutions for participation in these studies. Payments are made through the main member institution. For more information, consult the "Study Funding List" on the CALGB website ("members only" Financial section). You may also contact Mary A. Sherrell, Financial Officer at (773) 702-9856.

9170 Hospital vs Early Discharge Therapy of Low-Risk Patients with Fever and Neutropenia. Multi-Center Phase III Study.

9270 Colorectal Adenoma Chemoprevention Trial Using Aspirin. Phase III Study.

9334 Sclerosis of Pleural Effusion by Talc Thoracoscopy vs. Talc Slurry. Phase III Study.

9335 Video-assisted Wedge Resection + Radiotherapy for High Risk T1 NSCLC. Phase II Study.

9371 Weight Loss Program of Women with Breast Cancer. Pilot Feasibility Study.

9380 Thoracoscopic Staging for Esophageal Cancer. Phase II Study.

9431 Sequential and Concomitant Chemoradiotherapy with New Agents in Combination with Cisplatin for Inoperable Stage IIIA and IIIB NSCLC. Randomized Phase II Study.

9473 Omega-3 Fatty Acids for Cancer Cachexia. Phase I/II Trial.

9480 Suramin Dose Comparison Administered with a Fixed Dosing Schedule in Patients with Advanced Prostate Cancer. Phase III Study.

9481 Hepatic Artery Floxuridine, Leucovorin, and Dexamethasone vs Systemic 5-FU and Leucovorin as Treatment for Hepatic Metastases from Colorectal Cancer. Phase III Study.

9484 Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data. Specialized Registry.

9490 Does an Oral Analgesic Protocol Improve Pain Control for Patients with Cancer? (ECOG E4293)

9499 Chemoprevention Trial to Prevent Second Primary Tumors with Low-Dose 13-CIS Retinoic Acid in Head and Neck Cancer. (MDACC DM90-094)

9581 Adjuvant Immunotherapy with Monoclonal Antibody 17-1A after Resection for Stage B2 Colon Adenocarcinoma. Phase III Randomized Study.

9594 Intermittent Androgen Deprivation in Patients with Stage D2 Prostate Cancer. Phase III Study. (SWOG 9346)

9596 Vincristine, Doxorubicin, and Dexamethasone with or w/o PSC-833 in Patients with Relapsing or Refractory Multiple Myeloma. Phase III Study. (ECOG E1A95)

9670 Barriers to Participation of Older Women with Breast Cancer in Clinical Trials. Pilot Study.

9682 Prognostic Significance of Endorectal MRI in Predicting Outcome After Combined Radiation and Androgen Suppression for Prostate Cancer. Prospective Phase II Study.

9730 Taxol vs. Taxol + carboplatin for advanced NSCLC. Randomized Phase III Study.

9770 High-Dose vs Conventional Dose Octreotide Acetate vs Loperamide in the Treatment of Chemotherapy-related Diarrhea in Patients with Colorectal Cancer. Randomized Trial. (ECOG E1295)

CALGB 9342: A Randomized Trial of Three Doses of Paclitaxel in Patients With Metastatic Breast Cancer

Eric Winer, Donald Berry, David Duggan, I. Craig Henderson, Constance Cirrincione, M. Robert Cooper, Larry Norton, for the Cancer and Leukemia Group B

From the Dana-Farber Cancer Institute, Boston, MA; Duke University Medical Center, Durham, NC; Syracuse University of New York, Syracuse, NY; University of California San Francisco, San Francisco, CA; Wake Forest University - Bowman Gray School of Medicine, Winston-Salem, NC; Memorial Sloan-Kettering Cancer Center, New York, NY.

Between January 1994 and July 1997, 475 patients with metastatic breast cancer were randomized to receive paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) at 175, 210, or 250 mg/m^2 as a 3-hour infusion every 3 weeks without initial growth factor support. Eligibility criteria included performance status ≤2, measurable disease, adequate bone marrow reserve, SGOT ≤3X normal, and 0 or 1 prior chemotherapy regimens for metastatic disease. Median age of study subjects was 63 years; 90% had a performance status of 0 or 1; 115 (24%) of patients had received no prior chemotherapy in the metastatic setting. Disease measurements were repeated every three cycles, and treatment was continued until disease progression. In the first analysis of the trial results, there is no statistically significant relationship between paclitaxel dose and disease response (logistic regression) or survival (Cox regression). There is a significant correlation (P=.001) between paclitaxel dose and time to disease progression.

	Paclitaxel Dose			
	175 mg/m^2	210 mg/m^2	250 mg/m^2	P value
Response rate (95% CI)	21% (15-29%)	26% 19-35%	21% (14-21%)	NS
Median survival	10.7 months	11.7 months	12.7 months	0.44
Time to disease progression	3.9 months	4.2 months	5.4 months	0.001

In a proportional hazards model, higher paclitaxel dose, fewer sites of disease, and greater self-reported social support are significant predictors of longer time to progression. Toxicity is increased in the higher dose arms. Grade 3 sensory neuropathy developed in 8% of patients on 175 mg/m^2 paclitaxel, 18% on 210 mg/m^2, and 31% on 250 mg/m^2 (P<0.001). Treatment was discontinued due to toxicity in 5%, 9%, and 19% of patients on the 175, 210, and 250 mg/m^2 arms, respectively. Despite the greater degree of toxicity, formal quality-of-life analysis reveals no difference in patient-rated quality of life across the three arms. In conclusion, higher doses of paclitaxel do not improve response or survival in patients with metastatic breast cancer. Although there is a longer time to progression with higher doses, this potential advantage must be considered carefully in light of the greater toxicity seen with increasing dose.

National Surgical Adjuvant Breast Project Studies With Paclitaxel and Trastuzumab

Eleftherios Mamounas, John Bryant, Barry Lembersky, Elizabeth Tan-Chiu, D. Lawrence Wickerham, and Norman Wolmark

From the Mt. Sinai Medical Center, Cleveland, OH; NSABP Biostatistical Center, Pittsburgh, PA; and NSABP Operations Center, Pittsburgh, PA.

The National Surgical Adjuvant Breast Project (NSABP) recently completed a randomized trial in patients with positive axillary lymph nodes evaluating sequential administration of paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) following standard (AC) chemotherapy. Paclitaxel was administered at a dose of 225 mg/m^2 as a 3-hour infusion. Tamoxifen was also given concomitantly with chemotherapy in all patients 50 years of age or greater and in those less than 50 years of age with tumors that were positive for estrogen or progesterone receptors. Between August 1995 and May 1998, 3,060 patients were accrued. The mean time on study as of June 1998 is 16.3 months for both treatment groups. Patient characteristics are well balanced between treatment groups. About half of the patients were less than 50 years of age at the time of randomization. While about 70% of patients had 1 to 3 positive axillary nodes, only 4% of patients had more than 10 positive nodes. About two thirds of the tumors tested positive for estrogen or progesterone receptors. Overall toxicity was acceptable for the adjuvant setting. Grade 4 toxicity was more common during AC treatment (10% of patients) than during paclitaxel treatment (3%). Granulocytopenia on the first day of each chemotherapy cycle was minimal, with only 8% of patients experiencing grade 3/4 granulocytopenia during AC and 5% during paclitaxel. Febrile neutropenia was more frequent during AC (6% of patients) than during paclitaxel (2% of patients). Severe or life-threatening infection was uncommon (4% of patients during AC and 1% of patients during paclitaxel). Fifteen percent of patients experienced severe neurosensory toxicity during paclitaxel treatment. Severe hypersensitivity reactions were uncommon with paclitaxel (1%). Severe arthralgia/myalgia was seen in 12% of patients during paclitaxel treatment. Whereas 98% of patients in the AC group completed all four cycles of their assigned therapy, 79% of patients in the AC-paclitaxel group were able to complete all eight cycles of their assigned therapy.

With the development of trastuzumab, a humanized monoclonal antibody against the HER-2/*neu* oncogene, and the demonstration of its activity in patients with metastatic breast cancer who overexpress this oncogene, significant interest has developed in moving this agent into the adjuvant setting. However, the significant cardiotoxicity noted in the phase III trial when trastuzumab was combined with AC is of concern when adjuvant studies are being considered. This is of particular importance because there is increasing evidence that patients overexpressing the HER2/*neu* oncogene not only benefit from trastuzumab but also benefit from the administration of an anthracycline-based regimen. The NSABP is currently in the process of developing an adjuvant trial that will compare the sequential AC-paclitaxel regimen to the same regimen plus trastuzumab given for 1 year starting with the first cycle of paclitaxel. This study will be conducted in two parts. The first part will consist of a cardiac toxicity evaluation phase, and the second phase will evaluate the efficacy endpoints (disease-free and overall survival). A comprehensive cardiac monitoring plan has been developed for the first part of the study. The second part of the study will be implemented unless the first part demonstrates that there is more than 5% serious cardiotoxicity in the AC-paclitaxel plus trastuzumab group over and above the AC-paclitaxel group. This study is expected to open in the summer of 1999.

Sequential Dose-Dense Doxorubicin, Paclitaxel, and Cyclophosphamide for Resectable High-Risk Breast Cancer: Feasibility and Efficacy

By C. Hudis, A. Seidman, J. Baselga, G. Raptis, D. Lebwohl, T. Gilewski, M. Moynahan, N. Sklarin, D. Fennelly, J.P.A. Crown, A. Surbone, M. Uhlenhopp, E. Riedel, T.J. Yao, and L. Norton

Purpose: **Dose-dense chemotherapy is predicted to be a superior treatment plan. Therefore, we studied dose-dense doxorubicin, paclitaxel, and cyclophosphamide (A → T → C) as adjuvant therapy.**

Methods: **Patients with resected breast cancer involving four or more ipsilateral axillary lymph nodes were treated with nine cycles of chemotherapy, using 14-day intertreatment intervals. Doses were as follows: doxorubicin 90 mg/m² × 3, then paclitaxel 250 mg/m²/24 hours × 3, and then cyclophosphamide 3.0 g/m² × 3; all doses were given with subcutaneous injections of 5 μg/kg granulocyte colony-stimulating factor on days 3 through 10. Amenorrheic patients with hormone receptor-positive tumors received tamoxifen 20 mg/day for 5 years. Patients treated with breast conservation, those with 10 or more positive nodes, and those with tumors larger than 5 cm received radiotherapy.**

Results: **Between March 1993 and June 1994, we enrolled 42 patients. The median age was 46 years (range, 29 to 63 years), the median number of positive lymph nodes was eight (range, four to 25), and the median tumor size was 3.0 cm (range, 0 to 11.0 cm). The median intertreatment interval was 14 days (range, 13 to 36 days), and the median delivered dose-intensity exceeded 92% of the planned dose-intensity for all three drugs. Hospital admission was required for 29 patients (69%), and 28 patients (67%) required blood product transfusion. No treatment-related deaths or cardiac toxicities occurred. Doxorubicin was dose-reduced in four patients (10%) and paclitaxel was reduced in eight (20%). At a median follow-up from surgery of 48 months (range, 3 to 57 months), nine patients (19%) had relapsed, the actuarial disease-free survival rate was 78% (95% confidence interval, 66% to 92%), and four patients (10%) had died of metastatic disease.**

Conclusion: **Dose-dense sequential adjuvant chemotherapy with doxorubicin, paclitaxel, and cyclophosphamide (A → T → C) is feasible and promising. Several ongoing phase III trials are evaluating this approach.**

J Clin Oncol 17:93-100. © 1999 by American Society of Clinical Oncology.

COMBINATION CHEMOTHERAPY WITH cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or similar regimens modestly reduces the risks of relapse and death for patients with operable primary breast cancer.[1] Although some are widely used, no other regimen, including anthracycline combinations, has been consistently found to be greatly superior to CMF.[2-5]

In an attempt to improve upon these results, various manipulations of dose and the schedule of administration have been tested. Dose-intensification has generated great research interest over the last decade. The term dose-intensity was formulated and popularized as body size–adjusted dose (usually mg/m²) divided by time (usually per week).[6] Part of the appeal of dose-intensity has been the experimental observation that cell killing can be increased for some agents and some tumor models by an increase in dose size.[7] In these laboratory models, anticancer drugs kill a fraction of cells (called log-kill), and this is constant regardless of the number of cells present when the drugs are administered. Dose escalation is effective because this fraction increases as dose increases. Because each agent in a combination of agents should add its own log-kill effect, enough cycles of enough drugs at high enough individual dose levels should kill a very high percentage, if not all, of the cells, but clinical results do not match this prediction.

Resistance is the hypothesized reason that some (if not all) breast cancers are not cured by combination drug regimens.[7-10] To overcome resistance, combination chemotherapy using several drugs simultaneously at full dosages or, when this is impossible, in rapid alternation was predicted to be superior and studied clinically.[11]

The lack of success with alternating therapy in breast cancer suggests that the underlying assumptions may be incorrect. For example, human solid tumors do not exhibit exponential growth but rather seem to grow in a Gompertzian pattern.[12] With the Gompertzian model, the doubling time is not constant but rather increases with increasing

From the Breast and Gynecologic Cancer Medicine Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY.

Supported in part by NCI Contract No. CM-07311 and NCI P50-CA68425 (Specialized Programs of Research Excellence). The authors are recipients of the following grants and awards: American Cancer Society Career Development Award (C.H. and J.P.A.C.), American Society of Clinical Oncology Career Development Award (A. Seidman and J.B.), and Physician Scientist Award (D.L.).

Address reprint requests to Clifford Hudis, MD, MSKCC, 1275 York Ave, Box 206, New York, NY 10024; Email hudisc@mskcc.org.

0732-183X/99/1701-0093$3.00/0

tumor size. When the Gompertzian model is in effect, preclinical cancers proliferate more rapidly than we would predict from observations of clinical cancers, and it takes less time for the preclinical cancer to reach clinical size than we would estimate for an exponential tumor. Similarly, tumor regrowth after subcurative therapy could be quite rapid after each cycle of treatment, so eradication of disease is difficult, even when all of the cells are "sensitive" to the drugs used.[13]

If we conceive of the whole breast cancer in an individual patient as a collection of different sublines with different proliferation rates and different sensitivities to treatment, it seems likely that eradicating some sublines by chemotherapy would leave others to grow, and these residual sublines would do so rapidly by virtue of their Gompertzian kinetics. Hence, very effective therapies, even those killing most of the cells present, could translate to only small increases in disease-free survival in the clinic.

An alternative model predicts that the best way to cure this heterogeneous mix of cells is to eradicate the more numerous, faster growing cells first. Next, therapy should be directed against the smaller population of slowly growing and therefore more resistant cells.[13] This is termed sequential therapy, and this approach has been proven clinically superior to the alternating plan.[14] Sequential use of single agents also facilitates dose escalation by avoiding overlapping toxicities, which increases the probability of eradicating the drug-sensitive subpopulations.[15,16] The most widely used method of increasing dose-intensity is dose escalation, which has been proven to be modestly successful for some drugs in some dose ranges.[17] However, the total impact of a therapy, from the first moment of treatment to the very end of the drug administration period, could be related to the cell kill for each dose, the length of time drugs are given, and the rate of tumor growth between treatments. If so, then a fixed cell kill achieved repeatedly at shorter time intervals should increase the overall impact of therapy. This concept and approach is called dose density.

Dose-dense treatments increase dose-intensity not by increasing the numerator (dose), as with dose escalation, but by decreasing the denominator (time). Although dose-intensity may be increased by dose escalation or by increasing the dose density or by both, an advantage of dose density is that it should work even if the dose-response relationship for the agents being used is not rising steeply in the feasible dose range. Because sequential therapy is by definition more dose-dense than alternative plans and was superior in earlier studies, we chose this approach for further development, using three active agents in breast cancer: doxorubicin, paclitaxel, and cyclophosphamide. These three drugs were chosen on the basis of their high single-agent activity and previous demonstrations that high doses could be administered in a dose-dense fashion.[14,18-21] In this article, we report the results of this pilot trial of sequential, dose-dense doxorubicin, paclitaxel, and cyclophosphamide (Fig 1).

METHODS

Eligibility requirements were as follows: patients had to have completely resected invasive breast cancer metastatic to four or more ipsilateral axillary lymph nodes; normal levels of serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, and carcinoembryonic antigen; normal cancer antigen 15–3 test results; and no evidence of disease on chest radiographs, nuclear bone scans, and contrast-enhanced computed tomography scans of the chest and abdomen. In addition, normal cardiac function was required, as demonstrated by echocardiogram or by nuclear gated heart scan and electrocardiogram. Patients with known cardiac conduction system abnormalities, serious medical illnesses, or an inability to give informed consent were excluded.

Treatment Plan

Nine cycles of chemotherapy were planned using 14-day intertreatment intervals. The first three treatments consisted of doxorubicin 90 mg/m^2, given by intravenous push; the second three treatments consisted of paclitaxel 250 mg/m^2, given as a 24-hour infusion (Taxol; Bristol-Myers Squibb, Princeton, NJ, supplied by the National Cancer Institute, Bethesda, MD); and the third three treatments consisted of cyclophosphamide 3.0 g/m^2, given as a 1-hour infusion (see Fig 1). All nine cycles of chemotherapy were supported by granulocyte colony-stimulating factor (G-CSF) (Neupogen; Amgen, Thousand Oaks, CA) at a dose of 5 μg/kg SC on days 3 through 10 inclusive. With cyclophosphamide, the use of mesna was permitted but not required. Treatment was started within 8 weeks of the date of the final local control procedure.

Actual body weight was used for body surface area (m^2) calculations, but patients who were more than 40% above their ideal weight were dosed using the corrected weight (actual weight plus the ideal weight divided by 2).

A complete blood count with leukocyte differential was performed before each cycle of chemotherapy and three times a week after each cycle. Weekly determinations of total bilirubin, SGOT, and alkaline phosphatase were obtained. After the completion of the doxorubicin, paclitaxel, and cyclophosphamide portions of therapy, cardiac safety was assessed by chest radiographs and cardiac ejection fraction determinations, using either nuclear scanning or echocardiography. A daily calendar was provided on which patients recorded all doses of G-CSF along with any symptoms. Nonhematologic toxicity was graded by a nurse clinician and a physician during review of the calendar at each pretreatment visit.

Dose Modifications

Doxorubicin. Treatment was delayed if on the scheduled day of administration, the granulocyte count was less than 1,500 or the platelet count was less than 100,000. Treatment was resumed when these minimal levels were achieved. Dose reductions of 25% were required for patients who developed neutropenic fever (absolute granulocyte count below 1,000/mL^3 at the time of a documented temperature of 38°C or higher) or a documented bacteremia. Doxorubicin was withheld for grade 2 or 3 mucositis, dysphagia, and diarrhea, but it was resumed at full dose when these toxicities resolved.

Paclitaxel. Treatment was delayed if the granulocyte count was less than 1,500 or the platelet count was less than 100,000 on the scheduled

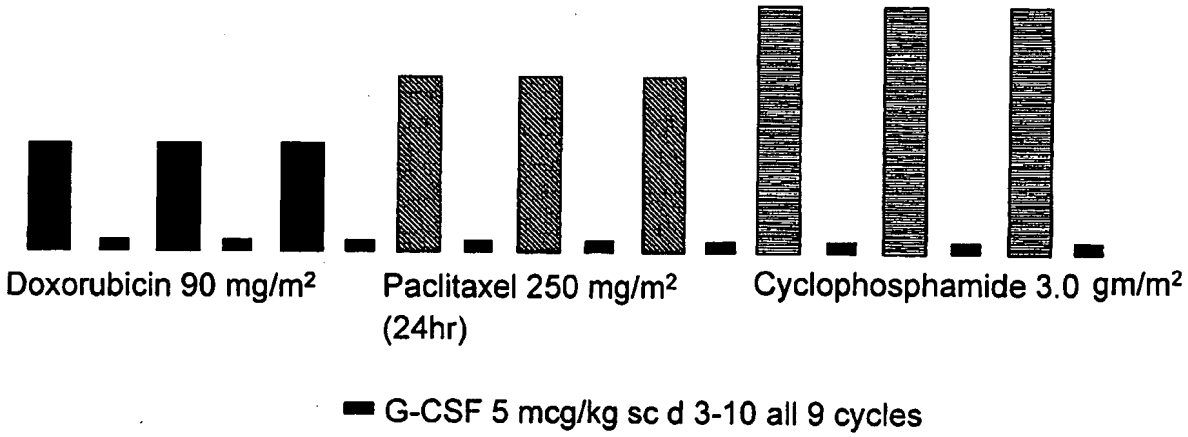

Fig 1. Treatment plan for sequential dose-dense therapy.

day of administration. Paclitaxel was resumed when these levels were achieved. Dose reductions of 20% (to 200 mg/m² and then to 160 mg/m²) were required for neutropenic fever and for any grade 3 nonhematologic toxicity attributable to a prior dose of paclitaxel.

Cyclophosphamide. No dose reductions were planned for cyclophosphamide. Instead, cyclophosphamide administration was delayed if the granulocyte count was less than 1,000 or the platelet count was less than 50,000 on the scheduled day of treatment. Treatment was resumed when these levels were achieved.

Granulocyte colony-stimulating factor. Administration of G-CSF was stopped when the absolute neutrophil count exceeded 75,000, but it was restarted when the count dropped to less than 10,000 if the drop occurred less than 10 days after the last dose of chemotherapy.

Radiotherapy

After mastectomy, patients with 10 or more involved axillary lymph nodes and patients whose tumor exceeded 5 cm in greatest diameter received chest wall radiotherapy. Patients treated with breast conservation also underwent radiation therapy. Standard dosing guidelines and techniques were used, and treatment was started approximately 4 weeks after the last dose of cyclophosphamide.

Tamoxifen

All patients who were amenorrheic at the end of chemotherapy and whose tumors expressed either (or both) the estrogen or progesterone receptor were placed on a 5-year course of tamoxifen 20 mg/day beginning approximately 4 weeks after the last dose of cyclophosphamide.

Follow-Up

To obtain the most accurate and conservative estimate of outcome and to monitor long-term toxicities, patients were followed closely after they completed chemotherapy. Histories and physical examinations were repeated at 3-month intervals, along with complete blood count, SGOT, alkaline phosphatase, carcinoembryonic antigen, and cancer antigen 15–3 tests. Chest radiographs, nuclear bone scans, and computed tomography scans of the chest and abdomen with contrast were obtained yearly. Any abnormal result prompted further investigation. Diagnosis of stage IV disease required tissue confirmation if possible.

Biostatistics

Dose-intensity. For each patient, the delivered dose-intensity for all three drugs was calculated by adding the total dose administered (per meter squared) and dividing by the number of weeks of treatment. For doxorubicin, the treatment duration was from the first day of doxorubicin until the first day of paclitaxel. For paclitaxel, the treatment duration was from the first day of paclitaxel until the first day of cyclophosphamide. For cyclophosphamide, the treatment duration was from the first day of cyclophosphamide until 14 days after the third (final) treatment.

Disease-free survival. Actuarial disease-free survival was calculated using the method of Kaplan and Meier,[22] starting from the date of local control surgery. Any recurrence of disease at any site (including ipsilateral and contralateral breast cancer) constituted a recurrence.

RESULTS

Between March 1993 and June 1994, 42 patients were enrolled in the study (see Table 1). One patient was removed from the study when she developed a recurrence in her mastectomy scar on day 29 when she presented for her third dose of doxorubicin. She was not assessable for feasibility but was included in the disease-free survival analysis. Two additional patients refused the last dose of cyclophosphamide. Thus, all but three patients (7%) received all nine planned chemotherapy treatments, and 41 patients (98%) were assessable for feasibility.

Hematologic Toxicity

Hematologic toxicity was marked but varied distinctly among the three agents (see Table 2). The incidence of neutropenic fever was greatest during treatment with doxorubicin and cyclophosphamide, whereas the requirement for packed RBC transfusion rose with increased cycles of treatment and was greatest during cyclophosphamide treatment. Platelet transfusion was necessary in four patients (10%) but only during the final cycles of cyclophosphamide. Overall,

Table 1. Descriptive Data

No. of patients enrolled	42
Age, years	
Median	46
Range	29-63
Positive nodes	
No.	8
Range	4-23
Tumor size, cm	
Median	3.0
Range	0-7
Modified radical mastectomy	
No.	31
%	74
Estrogen and/or progesterone receptor-positive	
No.	28
%	67
Treated with tamoxifen	
No.	25*
%	49
Treated with radiotherapy	
No.	24
%	57

*Three patients refused treatment with tamoxifen.

the majority of patients (69%) developed neutropenic fever, with 39% experiencing more than one episode, and 67% required transfusions of packed RBCs. All patients had full recovery of their peripheral blood counts at the conclusion of treatment. Prolonged follow-up has not revealed evidence of prolonged cytopenia.

Nonhematologic Toxicity

Grade 2 alopecia was universal. Other nonhematologic toxicities were frequent but mild, as shown in Table 3. There were no grade 4 nonhematologic toxicities, but specific grade 3 toxicities, including fatigue, bone pain, and stomatitis, were seen in up to 24% of patients. There was no clinically significant cardiac toxicity. All premenopausal patients became amenorrheic after completion of chemotherapy.

Dose-Intensity

The planned dose-intensity was 45 mg/m^2/week for doxorubicin, 125 mg/m^2/week for paclitaxel, and 1,500 mg/m^2/week for cyclophosphamide. As shown in Table 4, the median delivered dose-intensity for all three agents exceeded 92% of planned. For paclitaxel and cyclophosphamide, it exceeded 98%. For these calculations, the patient who experienced disease progression during the second cycle of doxorubicin was excluded, but the two patients who did not receive the third cycle of cyclophosphamide were included with an assumption that their third treatment would have required an additional 14 days. Thus, the delivered dose-intensity of cyclophosphamide was decreased by one third in these two patients.

Disease-Free Survival

At the time of analysis, the median duration of follow-up from the date of definitive local control surgery was 48 months (range, 3 to 57 months). In addition to the patient with early recurrence, eight other patients (21%) relapsed. Three relapses (7%) occurred in the central nervous system on days 254, 259, and 537, and four relapses (7%) occurred in soft tissues and/or viscera on days 551, 602, 768, and 1378. There was one bone-only relapse on day 819 (27 months). The median disease-free survival has not been reached. At the median follow-up of 48 months, the actuarial disease-free survival rate was 78% (95% confidence interval, 66% to 92%) (see Fig 2). The follow-up period for the 33 patients who showed no evidence of relapse ranged from 44 to 57 months. Four patients (10%) have died of disease progression.

Table 2. Hematologic Toxicity

	Doxorubicin	Paclitaxel	Cyclophosphamide	Total
No. of assessable cycles	125	123	121	369
No. of assessable patients	42	41	41	41
Nadirs				
WBC				
Median	1.2	3.3	0.4	
Range	0.5-5	0.2-16.5	0-3.3	
ANC				
Median	0.4	2.1	0.1	
Range	0-2.9	0-7.5	0-2.6	
Platelets				
Median	102	126	72	
Range	19-234	53-292	8-240	
Hemoglobin				
Median	9.4	8.3	7.3	
Range	7.5-11.6	5.6-10	4.4-9	
Intertreatment interval, days				
Median	14	14	14	
Range	13-30	11-35	11-36	
Hospitalizations				
No. of cycles	31	12	29	72
%	25	10	24	19
No. of patients	17	10	16	29
%	40	24	39	69
Transfusions				
PRBC				
No. of patients	4	10	21	28
%	10	24	51	67
Platelet				
No. of patients	0	0	4	4
%			10	10

Abbreviations: ANC, absolute neutrophil count; PRBC, packed red blood cells.

Table 3. Nonhematologic Toxicity: Overall Incidence of Grade 3 Toxicities

Toxicity	Incidence (%)
Fatigue	24
Bone pain	24
Stomatitis	17
Dermatitis	12
Neurosensory	15
Nausea	12
Joint pain	10
Diarrhea	7
Vomiting	5
Dyspnea	5
Myalgia	5
Edema	2

DISCUSSION

Adjuvant systemic chemotherapy prevents less than half of the expected relapses in early-stage breast cancer.[1] Increased dose-intensity and the addition of non–cross-resistant agents are two maneuvers predicted to improve the effectiveness of treatment, and this pilot study addresses both: Dose-intensification was achieved by combining dose escalation with increased dose density, and a newer, non–cross-resistant agent, paclitaxel, was incorporated.

The feasibility of the sequential application of dose-dense therapy is demonstrated by this pilot study, as we reported previously.[23] Presently, with a median follow-up exceeding 4 years on this nonrandomized trial, the disease-free survival rate of 78% is extremely promising and merits continued study of the principle of dose density, even as we continue to explore and learn more about the value of dose escalation.

It is important to emphasize that comparisons with other randomized and nonrandomized data sets are difficult and could easily be misleading. However, to justify continued study, the results of this pilot study should, at minimum, approach or exceed historic outcomes. In this regard, one basis for comparison is the sequential versus alternating chemotherapy trial from Milan.[14] In the Milan study, women with resected breast cancer metastatic to four or more nodes were randomly assigned treatment consisting of alternating CMF and doxorubicin (represented as CCACCACCACCA) or sequential (ie, more dose-dense) therapy, with all four cycles of doxorubicin preceding all eight cycles of CMF (represented as AAAACCCCCCCC). The sequential therapy arm was superior, and at 5 years (comparable to our follow-up time), the disease-free survival rate was 61% for 179 patients with an average of nine involved lymph nodes.[24] Another comparative data set could be any of the nonrandomized trials of high-dose, autologous stem cell-supported consolidation, including one from Duke University reporting 81% disease-free survival for women with four to nine positive nodes at 2-year follow-up.[25] Finally, in the Cancer and Leukemia Group B trial (CALGB 8541), patients with four or more positive nodes treated with higher-dose cyclophosphamide, doxorubicin, and fluorouracil had an approximately 67% disease-free survival rate at 3.4 years.[17] Taken together, these data suggest that our result is at least similar to others and certainly could be superior.

Table 4. Delivered Dose-Intensity (N = 41)

	Doxorubicin	Paclitaxel	Cyclophosphamide
Planned dose (mg/m² every 14 days × 3)	90	250/24 h	3,000
Planned dose-intensity (mg/m²/6 weeks)	45	125	1,500
Delivered dose-intensity (mg/m²/6 weeks)			
Median	43	123	1,484
Range	33-46	75-134	972-1,689
No. of dose reductions (%)	4 (10)	5 (12)	0
No. of dose omissions (%)	0	0	2 (5)

The pilot trial we present here used higher doses than are considered standard by many clinicians, and it is not clear that these more toxic dose levels are beneficial. In fact, if this regimen is ultimately proven superior, it could be because of the inclusion of paclitaxel and/or the use of more frequent dosing. Nonetheless, for doxorubicin, our planned dose-intensity was 45 mg/m²/week. By comparison, the dose-intensity for doxorubicin as part of the doxorubicin/cyclophosphamide (AC) regimen is 20 mg/m²/week.[26] The highest-dose arm of the now-completed CALGB-led Intergroup trial (93–44) planned for only 30 mg/m²/week (90 mg/m² every 21 days). At 18-month follow-up, the available randomized data did not suggest an advantage for doses of more than 60 mg/m², making the value of our level of doxorubicin questionable.[27]

For cyclophosphamide, our planned dose-intensity of 1,500 mg/m²/week also exceeds that of other standard regimens. In comparison, the planned dose-intensity for this agent is 200 mg/m²/week when intravenous CMF is given at 21-day intervals, and it was 800 mg/m²/week on the highest-dose arm of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-25.[28] Comparisons of dose-intensity with high-dose, stem cell-supported regimens are more difficult, because in some regimens either the drugs are given only once (although typically in divided doses over one or several days) or the dose-intensity is diluted by including the standard-dose combination therapy preceding the transplant in the calculation. Again, recent data from NSABP B-22 and B-25, which tested doses of cyclophosphamide from 600 mg/m² every 21 days × 4 up to 2,400 mg/m², do not yet suggest clear advantage for the latter.[28,29]

Until recently, the dose-intensification for paclitaxel was less studied than that for doxorubicin and cyclophosphamide

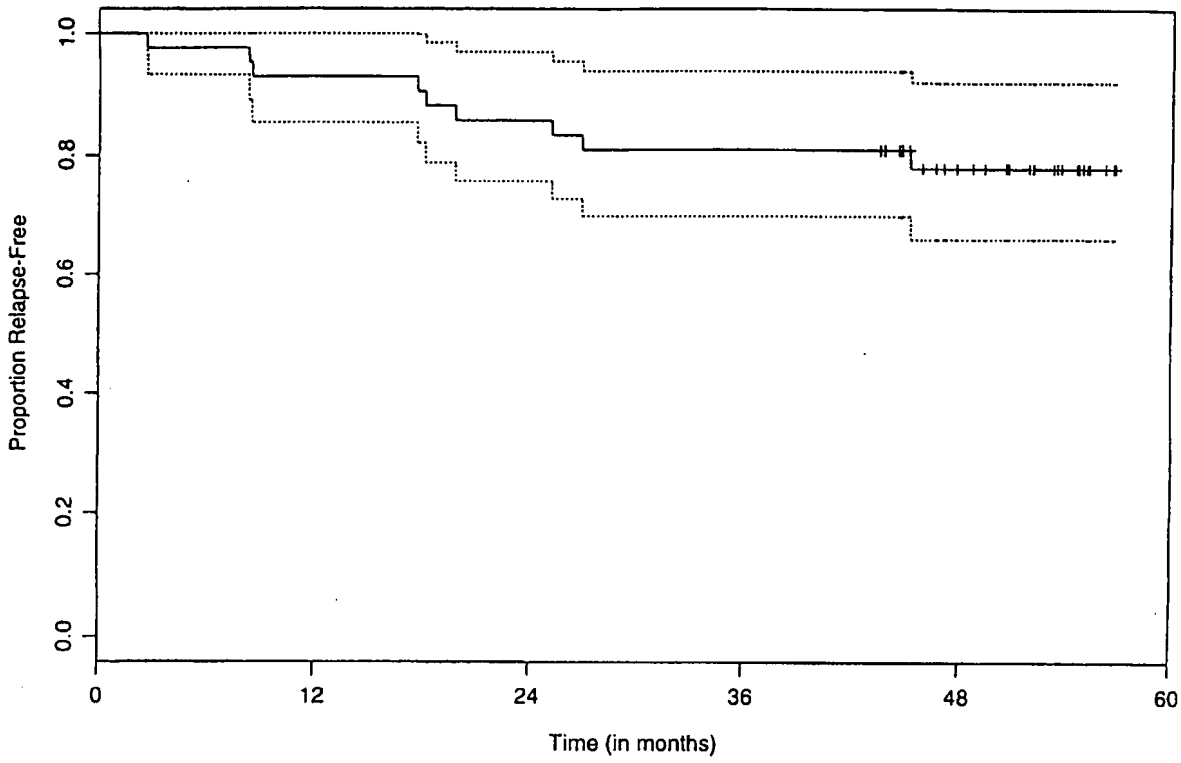

Fig 2. Disease-free survival using the method of Kaplan and Meier (with 95% confidence limits).

and was complicated by the duration of infusion. Now, however, for advanced disease, there seems to be an advantage for 175 mg/m^2 compared with 135 mg/m^2 when it is administered over 3 hours, and even higher doses may offer a small additional benefit.[30,31] An advantage for longer infusion durations is also possible, although not completely resolved.[32-34] With no confirmation that lower doses and 3-hour infusions were equivalent to higher doses and longer infusions, and on the basis of the earlier clinical trials of paclitaxel, we chose to use the latter in this pilot trial. However, if 3-hour infusions are ultimately proven equivalent to 24-hour infusions, then the less toxic, shorter infusion schedule could be substituted.

On the basis of our demonstration of feasibility for dose-dense chemotherapy and our promising disease-free survival rates, several studies have been designed to build on our results. The American Intergroup is currently accruing to a Southwest Oncology Group-coordinated trial (96–23) comparing a regimen similar to the one we report here with conventional chemotherapy (AC) followed by a single cycle of high-dose chemotherapy rescued by autologous hematopoietic stem cell reinfusion in patients with four to nine involved nodes. Because of our experience with toxicity and a separate subsequent randomized trial we conducted, the doxorubicin and paclitaxel doses on the sequential dose-dense arm of this trial were reduced slightly to 80 mg/m^2 and 200 mg/m^2, respectively.

The recently closed Intergroup study coordinated by the CALGB (93–44) asked not only whether escalated dose levels of doxorubicin improve disease-free or overall survival of patients with node-positive primary breast cancer, but also whether sequential chemotherapy with paclitaxel after AC conveys therapeutic benefit. On the basis of the safety of AC followed by paclitaxel, the recently reported lack of benefit with escalated doses of doxorubicin, and the superiority of adding paclitaxel, the CALGB is coordinating the next node-positive Intergroup trial (CALGB 97–41), in which all patients will receive doxorubicin, paclitaxel, and cyclophosphamide at standard doses. On the basis of CALGB 93–44 as well as the NSABP B-22 and B-25 trials discussed above, the doses of doxorubicin, paclitaxel, and cyclophosphamide are fixed at 60, 175 (over 3 hours), and 600 mg/m^2, respectively, for all patients.[27,29,35] The design is factorial 2 × 2: one avenue of questioning will compare the

use of AC followed by paclitaxel with the sequential use of doxorubicin, paclitaxel, and cyclophosphamide; the other line of questioning will compare the administration of drugs every 2 weeks (as allowed by the use of G-CSF) with the conventional 3-week schedule (in the latter case, G-CSF is permitted only when febrile neutropenia complicates therapy). Importantly, this new 2 × 2 Intergroup trial has been designed to address principles rather than specific regimens, and the answers to the questions being asked should be valid and informative even if we later learn that different dose levels or infusion durations (in the case of paclitaxel) are superior to the dose levels that we used in the trial described in this article.

Dose-dense therapy using sequential doxorubicin, paclitaxel, and cyclophosphamide at escalated doses is feasible and associated with a promising disease-free survival result. Wider use of this specific regimen requires appropriate randomized study, as is now ongoing. As we better define the optimal dose levels for routine use, the concepts underlying this pilot study could have even broader application, as will be determined from the randomized trials we have described.

REFERENCES

1. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group. Lancet 339:1-15, 71-85, 1992

2. Fisher B, Redmond C, Wickerham DL, et al: Doxorubicin-containing regimens for the treatment of stage II breast cancer: The National Surgical Adjuvant Breast and Bowel Project experience. J Clin Oncol 7:572-582, 1989

3. Misset J, Palma M, Delgado M, et al: Adjuvant treatment of node-positive breast cancer with cyclophosphamide, doxorubicin, fluorouracil, and vincristine versus cyclophosphamide, methotrexate, and fluorouracil: Final report after a 16-year median follow-up duration. J Clin Oncol 14:1136-1145, 1996

4. Coombes RC, Bliss JM, Wils J, et al: Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide in premenopausal women with axillary node-positive operable breast cancer: Results of a randomized trial. J Clin Oncol 14:35-45, 1996

5. Carpenter JT, Velez-Garcia E, Aron BS, et al: Five-year results of a randomized comparison of cyclophosphamide, doxorubicin (adriamycin), and fluorouracil (CAF) vs. cyclophosphamide, methotrexate and fluorouracil (CMF) for node positive breast cancer: A Southeastern Cancer Study Group study. Proc Am Soc Clin Oncol 13:66, 1994 (abstr 68)

6. Hryniuk W, Levine MN: Analysis of dose intensity for adjuvant chemotherapy trials in stage II breast cancer. J Clin Oncol 4:1162-1170, 1986

7. Skipper H, Schabel FJ, Wilcox W: Experimental evaluation of potential anticancer agents XIII: On the criteria and kinetics associated with "curability" of experimental leukemia. Cancer Chemother Rep 35:1, 1964 (abstr)

8. Law L: Origin of resistance of leukaemic cells to folic acid antagonists. Nature 169:628, 1952 (abstr)

9. Goldie J, Coldman A: Application of theoretical models to chemotherapy protocol design. Cancer Treat Rep 70:127-131, 1986

10. Luria S, Delbruck M: Mutations of bacteria from virus sensitivity to virus resistance. Genetics 28:491, 1943 (abstr)

11. Goldie JH, Coldman AJ, Gudauskas GA: Rationale for the use of alternating non-cross-resistant chemotherapy. Cancer Treat Rep 66:439-449, 1982

12. Norton L: A Gompertzian model of human breast cancer growth. Cancer Res 48:7067-7071, 1988

13. Surbone A, Gilewski T, Norton L: Cytokinetics, in: Holland JF, Bast RC Jr, Morton DL, et al (eds): Cancer Medicine, Vol 1 (ed 4). Baltimore, MD, Williams & Wilkins, 1996, pp 769-798

14. Bonadonna G, Zambette M, Valagussa P: Sequential or alternating doxorubicin and CMF regimens in breast cancer with more than three positive nodes. JAMA 273:542-547, 1995

15. Peters WP, Ross M, Vredenburgh JJ, et al: High-dose chemotherapy and autologous bone marrow support as consolidation after standard-dose adjuvant therapy for high-risk primary breast cancer. J Clin Oncol 11:1132-1143, 1993

16. Crown J, Kritz A, Vahdat L, et al: Rapid administration of multiple cycles of high-dose myelosuppressive chemotherapy in patients with metastatic breast cancer. J Clin Oncol 11:1144-1149, 1993

17. Wood W, Budman D, Korzun A, et al: Dose and dose intensity trial of adjuvant chemotherapy for stage II, node-positive breast carcinoma. N Engl J Med 330:1253-1259, 1994

18. Bronchud MH, Howell A, Crowther D, et al: The use of granulocyte colony-stimulating factor to increase the intensity of treatment with doxorubicin in patients with advanced breast and ovarian cancer. Br J Cancer 60:121-125, 1989

19. Seidman A, Reichman B, Crown J, et al: Taxol plus recombinant human granulocyte colony stimulating factor as initial and as salvage chemotherapy for metastatic breast cancer: A preliminary report. J Natl Cancer Inst Monogr 15:171-175, 1993

20. Lichtman S, Ratain M, Van Echo D, et al: Phase I trial of granulocyte-macrophage colony-stimulating factor plus high-dose cyclophosphamide given every 2 weeks: A Cancer and Leukemia Group B study. J Natl Cancer Inst 85:1319-1326, 1993

21. Hudis C, Lebwohl D, Crown J, et al: Dose-intensive sequential crossover adjuvant chemotherapy for women with high risk node-positive primary breast cancer, in: Salmon SE (ed): Adjuvant Therapy of Cancer IV. Philadelphia, PA, JB Lippincott, 1993, pp 214-219

22. Kaplan E, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

23. Hudis C, Seidman A, Baselga J, et al: Sequential adjuvant therapy with doxorubicin/paclitaxel/cyclophosphamide for resectable breast cancer involving four or more axillary nodes. Semin Oncol 22:18-23, 1995 (suppl 15)

24. Buzzoni R, Bonadonna G, Valagussa P, et al: Adjuvant chemotherapy with doxorubicin plus cyclophosphamide, methotrexate, and fluorouracil in the treatment of resectable breast cancer with more than three axillary lymph nodes. J Clin Oncol 9:2134-2140, 1991

25. Hussein A, Plumer M, Vredenburgh J, et al: High-dose chemotherapy (HDC) with cyclophosphamide (C) cisplatin (P), and BCNU (B) (CPB) and autologous bone marrow (ABM) and peripheral blood progenitor cells (PBPCs) for stage II/III breast cancer involving 4–9 axillary lymph nodes. Proc Am Soc Clin Oncol 15:A1026, 1996

26. Fisher B, Brown AM, Dimitrov NV, et al: Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: Results from the National Surgical Breast and Bowel Project B-15. J Clin Oncol 8:1483-1496, 1990

27. Henderson I, Berry D, Demetri G, et al: Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (Pts) with node-positive primary breast cancer (BC). Proc Am Soc Clin Oncol 17:101a, 1998 (abstr 390a)

28. DeCillis A, Anderson S, Bryant J, et al: Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) on NSABP B-25: An update. Proc Am Soc Clin Oncol 16:130a, 1997 (abstr)

29. Fisher B, Anderson S, Wickerham D, et al: Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-22. J Clin Oncol 15:1858-1869, 1997

30. Nabholtz J-M, Gelman K, Bontenbal M, et al: Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. J Clin Oncol 14:1858-1867, 1996

31. Winer E, Berry D, Duggan D, et al: Failure of higher dose paclitaxel to improve outcome in patients with metastatic breast cancer: Results from CALGB 9342. Proc Am Soc Clin Oncol 17:101a, 1998 (abstr 388)

32. Seidman A, Hochhauser D, Gollub M, et al: Ninety-six- hour paclitaxel infusion after progression during short taxane exposure: A phase II pharmacokinetic and pharmacodynamic study in metastatic breast cancer. J Clin Oncol 14:1877-1884, 1996

33. Holmes F, Valero V, Walter R, et al: Phase III trial of paclitaxel administered over 3- or 96-hours for metastatic breast cancer. Proc Am Soc Clin Oncol 15:106, 1996 (abstr 91)

34. Mamounas E, Brown A, Smith R, et al: Effect of taxol duration of infusion in advanced breast cancer (ABC): Results from NSABP B-26 trial comparing 3- to 24-hr infusion of high-dose taxol. Proc Am Soc Clin Oncol 17:101a, 1998 (abstr 389)

35. Wolmark N, Fisher B, Anderson S. The effect of increasing dose intensity and cumulative dose of adjuvant cyclophosphamide in node positive breast cancer: Results of NSABP B-25. Breast Cancer Res Treat 46:26, 1997 (abstr)